JC07 Rec'd PCT/PTO 22 JAN 2001

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	ATTORNEY'S DOCKET NUMBER P66226US0
	US APPLICATION NO. (If known, see 37 CFR 1.5) 09/764990

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/FR99/01760	19 July 1999	20 July 1998

TITLE OF INVENTION

PHARMACEUTICAL COMPOSITION INTENDED IN PARTICULAR FOR THE PREVENTION AND THE TREATMENT OF RADIOMUCOSITIS AND CHEMOMUCOSITIS

APPLICANT(S) FOR DO/EO/US

Jerome BESSE, Tam NGUYEN and Joelle LEYDER

Applicant herein submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for Internatl. Preliminary Examination was made by the 19th month from earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☒ A translation of the annexes to the Internatl. Preliminary Examination report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:

    International Search Report - EPO
    PCT Request Form
    PCT/IB/304 Form
    First Page of Publication
    International Preliminary Examination Report - with annexes

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US APPLICATION NO (If known, see 37 CFR 1.5) 09/764990	INTERNATIONAL APPLICATION NO PCT/FR99/01760	ATTORNEY'S DOCKET NUMBER P66226US0

	CALCULATIONS	PTO USE ONLY
17. ☒ The following fees are submitted:		
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Internatl. prelim. examination fee paid to USPTO (37 CFR 1.492 (a) (1)) . . $690.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (2)) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) . . $710.00		
Neither international preliminary examination fee (37 CFR 1.492 (a) (3)) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO) **$1000.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (4)) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00		
Search Report prepared by the EPO or JPO (37 CFR 1.492 (a) (5)) **$860.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 860.00	
Surcharge of $130.00 for furnishing the **oath or declaration** later than ☐ **20** ☐ **30** months from the earliest claimed priority date (37 CFR 1.492(e)).	$	

Claims	**Number Filed**	**Number Extra**	Rate		
Total Claims	**8** - 20 =	-0-	x $18.00	$	
Independent Claims	**2** - 3 =	-0-	x $80.00	$	
Multiple Dependent Claim(s) (if applicable)			+ $270.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 860.00	
Reduction by 1/2 , Applicant qualifies for Small Entity Status.				$	
SUBTOTAL =				$ 860.00	
Processing fee of $130 for furnishing the **English translation** later than ☐ **20** ☐ **30** months from the earliest claimed priority date (37 CFR 1.492(f))				$	
TOTAL NATIONAL FEE =				$ 860.00	
Fee of $40.00 for recording the enclosed **assignment** (37 CFR 1.21(h)). Assignment must be accompanied by appropriate cover sheet (37 CFR 3.28, 3.31).				$ 40.00	
TOTAL FEES ENCLOSED =				$ 900.00	
				Amt. to be refunded:	$
				Amt. charged:	$

a. ☒ A check in the amount of $ 900.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. **06-1358** in the amount of $ --- to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge my account any additional fees set forth in §1.492 during the pendency of this application, or credit any overpayment to Deposit Account No. **06-1358**. A duplicate copy of this sheet is enclosed.

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By William E. Player
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JPH&S 3/95

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant(s): Jerome BESSE et al.

Serial No.: New

Filed: January 22, 2001

For: PHARMACEUTICAL COMPOSITION INTENDED IN PARTICULAR FOR THE PREVENTION AND THE TREATMENT OF RADIOMUCOSITIS AND CHEMOMUCOSITIS

PRELIMINARY AMENDMENT

Assistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE CLAIMS

Please cancel International Preliminary Examination Report Claims 1 through 12 and replace with amended claims 13 through 20 as listed on the attached page.

REMARKS

The foregoing Preliminary Amendment is requested in order to place the claims in better form for examnination.

Early action on the merits is respectfully requested.

Respectfully submitted,

JACOBSON, PRICE, HOLMAN & STERN, PLLC

By _____
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Date: January 22, 2001
Atty. Docket: P66226US0
WEP/cmf

13. Pharmaceutical composition intended to adhere to a mucous membrane in particular for the prevention and treatment of radiomucositis, and of chemomucositis induced by radiotherapy and combined radiochemotherapy, comprising an effective quantity of a compound chosen from flavonoids and isoflavonoids in the form of a mixture with a vehicle which is liquid at room temperature and which gels at the temperature of the mucous membrane and which is capable of adhering to the mucous membrane because of its gelled state.

14. Composition according to Claim 13 whose vehicle is an aqueous vehicle and comprises a mixture of 0.05 to 5% (preferably 0.1 to 3%) by weight of an agent conferring viscosity and of 1 to 20% (preferably 5 to 20%) by weight of an agent modifying the viscosity according to the temperature.

15. Composition according to Claim 14, in which the agent modifying the viscosity according to the temperature is chosen from poloxamers, poloxamines, and divinylbenzenesorbitol compounds.

16. Composition according to Claim 13, in which the flavonoid is chosen from rutosides, diosmin, quercitrin, tangeretin and hesperidin.

17. Composition according to Claim 13, in which the isoflavonoid is genistein, daidzin or glycitin.

18. Composition according to Claim 16, in which the rutoside is rutin.

19. Composition in solid form and forming a composition according to Claim 13 by mixing with water.

20. Method for the prevention and for the treatment of radiomucositis and of chemomucositis.comprising the administration on the mucous membrane of an effective amount of a compound chosen from flavonoids and isoflavonoids in the form of a mixture with a vehicle which is liquid at room temperature and which gels at the temperature of the mucous membrane and which is capable of adhering to this mucous membrane because of its gelled consistency.

"Pharmaceutical composition intended in particular for the prevention and the treatment of radiomucositis and chemomucositis"

The present invention relates to a pharmaceutical composition intended in particular for the prevention and the treatment of radiomucositis and of mucositis induced by anticancer polychemotherapies.

From the data collected during the period 1987-1992 among its member countries, the World Health Organization (WHO) calculated (for the year 1994) an estimation of the incidence of cancers, according to gender, on a global scale (World Health Organization: World Health Statistics Annuals, 1987-1992 - Geneva, Switzerland, WHO): in men, the location characterized by the highest incidence is the prostate (32%); in women, the highest incidence is breast cancer (32%). In men, cancers of the head and neck as well as of the oropharyngeal cavity have an incidence of close to 6% and the incidence of colorectal cancers is 12%. In women, the incidence of cancers of the "head and neck, and the oropharyngeal cavity" is 5% and that of colorectal cancer 13% while the incidence of uterine cancers is 8%. These figures speak for themselves and show immediately the extent of the problem posed by the taking into account of the side effects of antimitotic treatments used, in particular antiproliferative polychemotherapies and radiotherapy.

Depending on their location, cancer therapy frequently involves medium- or high-energy radiotherapy either as a first line treatment, or as an adjuvant therapy to surgery and chemotherapy. Radiotherapy is in particular widely used for the treatment of certain locations: head and neck; brain; oropharyngeal cavity; oesophagus and stomach; large intestine and rectum; uterus. In 1994, the incidence of new cases of cancer in these locations was estimated by the National Cancer Institute (NCI), for the population of the United States:

- head and neck, brain: 17,500 new cases

- oropharyngeal cavity: 29,600 new cases
- larynx: 12,500 new cases
- oesophagus and stomach: 35,000 new cases
- colon and rectum: 150,000 new cases
- uterus: 46,000 new cases.

By virtue of the advances in computerized axial tomography, the determination of irradiation fields, the kinetics of irradiation as well as the rates of radiation doses have been improved regularly. Accordingly, for "head and neck" cancers, it is now known that the period between surgical exeresis and radiotherapy should not exceed 6 weeks and that any interruption in the radiotherapy - even in the event of severe adverse effects - is prejudicial to its efficacy. Even more, it is known that certain tumours require an acceleration of the radiotherapy (dose intensification) in order to reach more effectively a larger number of tumour cells when these are in the dividing phase: this is hyperfractionated radiotherapy. In the same spirit, the constant search for potentiation of the therapeutic effect has led to the evaluation of alternate radiochemotherapy and to protontherapy which allows the irradiation to be very finely focused.

Radiotherapy-based irradiation of a cancer of the oesophagus or of the larynx leads to the appearance of a painful dysphagia, a source of an intense functional discomfort (which can cause substantial loss of weight), by attack on the mucous membrane by the ionizing radiation. Likewise, the irradiation of abdominal adenopathies or tumours induces complications at the gastric level. Nausea and vomiting are the most frequent manifestations. However, early epithelial impairments and in particular painful ulcerations, which are often very severe and which may persist after the end of the radiotherapy cycle, may appear.

However, it is the buccal complications of cervicofacial radiotherapy which are the most typical.

The initiation of this treatment is marked by a more or less intense mucosal reaction - oropharyngeal mucositis - which is similar to a very severe skin erythema, following a serious burn induced by prolonged exposure to intense ultraviolet radiation of solar origin (very hot summer season or tropical countries). The specificity of the radiomucositis, in particular oropharyngeal radiomucositis, is linked to the specificity of the mucous membrane and to its fragile nature. Unlike the skin integuments which are thick covering tissues, the mucous membranes (buccal, gingival, gastric, intestinal, uterine, vaginal and anorectal) are very fragile because they consist of cellular structures lacking keratin, which are very rich in water and in blood vessels. In such tissues, the molecular agitation induced by high-energy radiation causes an extremely rapid disorganization of the cellular organization which is at the origin of the destruction of the mucous membrane. Unlike the skin tissue, these mucous membranes are not resistant to attacks of this type and do not have any physiological system of protection (e.g.: lipohydrophilic character; rate of renewal, and the like) which is effective against the damage caused by the energy received during each irradiation cycle.

The most deleterious consequences of the oropharyngeal mucositis are the functional discomfort the perception of which can be extremely variable from one patient to another, this discomfort not being linked to the intensity of the clinical symptom. The radiomucositis may therefore be highly crippling, in particular when the erythema is followed by an oedema and then by erosions of the mucous membrane which can, in addition to intense pain, seriously hamper food intake.

In addition, irradiation of the salivary glands, taken in the target volume, causes drying of the mouth, which is often intense and long lasting, or even permanent. In addition to the discomfort of

hypoptyalism or of xerostomia (deprivation of saliva), which can also be extremely badly felt, multiple caries may also develop rapidly. At this stage, the major risk of dental lesions, apart from loss of teeth, is requiring the extraction of the tooth on an irradiated bone with the constitution of an osteoradionecrosis, which is essentially mandibular. Thus, the complications of post-irradiation xerostomia are mycoses, repeated bacteria infections, multiple caries and osteoradionecroses and these are frequent, in particular, during radiotherapies of the upper aerodigestive tracts.

Because the mucositis can be aggravated by several cofactors (e.g.: associated chemotherapy [5-FU, cisplatin], nicotine addiction, alcoholism, poor dentibuccal hygiene, and the like) the risks induced by the appearance of radiomucositis may be extremely serious. They therefore justify the search for means for the effective prevention of the erythematous mucosal reaction caused by ionizing radiation.

The authors of the present invention were interested in this question because the current therapeutic means for the prevention or treatment of radiomucositis are not optimized. Indeed, they involve essentially the simultaneous administration of analgesics (e.g.: aspirin), of antifungals (e.g.: amphotericin B, miconazole), of a contact anaesthetic (e.g.: xylocaine) and of mouthwash (based on chlorhexidine and hexamidine) which are systematically repeated.

This is how the idea emerged to develop a composition which is liquid at room temperature, but which is capable of adhering to a mucous membrane because of its passage to the gelled state when the temperatures reaches the temperature of the mucous membrane and which contains substances with anti-free radical activity, while not interfering with the energy emitted by each dose of radiotherapy. Developed to prevent the appearance of buccopharyngeal mucositis

following radiotherapy for "head and neck" cancers, this concept of a specifically adapted pharmaceutical preparation can also be applied to other forms of mucositis which are induced by radiotherapy and/or chemotherapy or alternatively combined radiochemotherapy in the treatment of cancers such as those of the colon, the rectum and the anus or when these therapies incidentally reach the vaginal mucous membrane.

The subject of the present invention is thus a pharmaceutical composition intended in particular for the prevention and the treatment of radiomucositis and of chemomucositis, comprising an effective quantity of a compound having anti-free radical activity in the form of a mixture with a vehicle which is liquid at room temperature and which gels at the temperature of the mucous membrane and which is capable of adhering to the mucous membrane because of its gelled state.

The compound having anti-free radical activity may be in particular chosen from:

1 - flavonoids of natural origin, for example:

i) flavonols or flavonolols, among which:

- a rutoside: rutin (quercitin 3-O-rutinoside), quercitrin (quercetin 3-O-rhamnoside), isoquercitrin (quercetin 3-O-glucoside),
- diosmin (diosmetin 7β-rutinoside), astragalin (kaempferol 3-O-glucoside), kaempferol 3-O-rutinoside, myricitrin (or myricetin 3-O-rhamnoside),
- robinin (or kaempferol 3-O-robinoside 7-rhamnoside),
- kaempferitrin (or kaempferol 3,7-O-dirhamnoside),
- nobiletin,
- tangeretin.

ii) flavones, among which:

- rhoifolin (or apigenin 7-O-neohesperidoside), luteolin 7-O-glucoside,
- scutellarin (or scutellarein 5-O-glucoside),
- pectolinarin (or pectolinarigenin 7-O-rutoside),
- galuteolin (or luteolin 5-O-glucoside),
- acaciin (or acacetin 7-O-rhamnoglucoside),

iii) **flavanones, among which:**

- liquiritin (or liquiritin 4'-O-glucoside), naringin (or naringenin 7-O-neohesperidoside), hesperidin (or hesperetin 7-O-rutinoside),
- eriodictin (or eridictiol 7-O-rhamnoside)

2 - **isoflavonoids of natural origin, for example:**

- formononetin 7-O-glucoside (or ononin), afromosin 7-O-glucoside (or wistin),
- genistein (or genistein 7-O-glucoside), daidzin, glycitin,
- genistein 6-O-malonylglucoside, daidzein 6-O-malonylglucoside, genistein 6-O-acetylglucoside,
- iridin (or irigenin 7-O-glucoside),
- irisolone,
- tectoridin (or tectorigenin 7-O-glucoside) or shekanin.

3 - **tocopherols;**

4 - **polyphenols and plant extracts containing polyphenols** such as procyanidolic oligomers, extracts of St. John's wort, of Kallanchoe pinnata, of camomile, of pine bark, of tea, of Centella asiatica, extracts of larch, of edelweiss,

5 - **vitamins:** for example, vitamin A, a carotenoid, alpha-lipoic acid,

6 - **the active fractions of vegetable oils** such as alpha-lupaline, hierogaline,

7 - **butylated hydroxyanisole, butylated hydroxytoluene.**

The vehicle which is liquid at room temperature and which gels at the temperature of the mucous membrane may consist in particular of an aqueous dispersion or solution of a mixture of:

a - 0.05 to 5% by weight (preferably from 0.1 to 3% by weight) of an agent conferring viscosity;

b - 1 to 20% by weight (preferably from 5 to 20% by weight) of an agent modifying the viscosity according to the temperature.

i) The agents conferring viscosity may be chosen in particular from the following compounds:

- colloids or hydrocolloids (polysaccharide substances and related substances):
  - galactomannans and derivatives: guar gum, carob gum, tara gum, and the like
  - starch and derivatives
  - gum arabic, tragacanth gum, karaya gum, and the like
  - pectins and derivatives of pectin, and the like
  - alginates: alginic acid, sodium alginate, sodium/calcium alginate, and the like
  - carrageenans and derivatives, and the like
  - cellulose and derivatives: carboxymethylcellulose (CMC), sodium carboxymethylcellulose, calcium CMC, methylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxyethylcellulose, and the like
  - high-molecular weight dextrans
  - xanthans and derivatives, and the like
  - hyaluronic acid and derivatives, chitin and chitosan and their derivatives, and the like
- polymers of acrylic and methacrylic acids and derivatives: polymethacrylate, carbophilic carboxyvinyl polymer (carbopol, carbomer), polyhydroxyethyl methacrylate,
- polyvinyl derivatives, polyvinylpyrrolidone, poly(vinylpyrrolidone and vinyl acetate), polyvinyl acetatephthalate, polyvinyl alcohol,

- high-molecular weight polyethylene glycols,
- polyacrylamide and derivatives,
- polymers of maleic acid, such as for example: copolymer of polyvinyl ether/maleic acid, sodium/calcium salts of the polyvinyl ether/maleic acid copolymer complex,
- sodium polystyrenesulphonate,
- inorganic derivatives: silica and silicate and silicone derivatives and the like

ii) As examples of agents modifying the viscosity according to the temperature, there may be mentioned:

- poloxamers (e.g.: poloxamer 188, poloxamer 407 and the like) and poloxamines
- compounds of the divinylbenzenesorbitol type (disorbene), which are soluble in lipophilic medium.

Compositions which have a viscosity of less than 200 x 10^{-3} Pa.s at room temperature (20°C) and a viscosity greater than 2000 x 10^{-3} Pa.s at 35-37°C are preferred, the viscosity being determined with an LV type Brookfield viscometer/LV4 rotor/speed of rotation 0.5 rpm/reading after 15 seconds.

By way of example, a solution according to the invention which contains a concentration of agent conferring viscosity - c = 1.7% of hydroxymethylpropyl-methylcellulose (HPMC), - with 5% of rutin and 14% of poloxamer 407, exhibits the following behaviour on raising the temperature:

Temperature (t°C)	Viscosity (10^{-3} Pa.s)
25	314
30	1433
35	3027

Thus, at 25°C the solution is fluid (viscosity of the order of 300x10^{-3} Pa.s) and the gelling is obtained by passage to a temperature of 30°C, then 35°C

(the viscosity is multiplied by 10 between 25 and 35°C).

The aqueous compositions preferably have pH values which are compatible with the mucous membranes (in general between pH 7 and 8).

The subject of the present invention is also compositions in solid form intended to be mixed with water to form a solution which is liquid at room temperature and which is capable of forming a gel on contact with the mucous membrane to be protected. For the gastric mucous membrane and/or the intestinal mucous membrane, it is thus possible to have solid forms such as a powder or a granule, or alternatively granules which give, upon addition to a liquid vehicle, a liquid composition (example: powder for syrup, for suspension or solution for oral administration to be prepared immediately before use). The compositions may also be provided in the form of bare tablets or granules to be dissolved in water just before use.

The compositions according to the invention may contain other active ingredients combined with the compounds having anti-free radical activity and in particular those belonging to the following pharmacotherapeutic families:

- analgesics and antispasmodics (paracetamol, aspirin, codeine, morphine, atropine, loperamide, phloroglucinol, and the like), anaesthetics (xylocaine, lidocaine) and antiseptics (chlorhexidine, hexamidine),
- anti-inflammatory agents belonging to the corticoid family (prednisolone, triamcinolone, and the like) or oxicams (e.g.: piroxicam, and the like),
- anti-ulcer agents (antihistamines H_2, prostaglandins and derivatives, proton pump inhibitors such as omeprazole, pantoprazole, lanzoprazole),
- antacids and gastrointestinal dressings (aluminium phosphate, aluminium and magnesium hydroxide, clays (diosmectites, actapulgites, and the like),

- medicaments for gastrooesophageal reflux and for digestive motivity (sodium alginate, sodium bicarbonate, metoclopramide, and the like),

- antiemetics (benzamides, antihistamines H_1, setrons, and the like),

- antidiarrhoeals (loperamide, and the like),

- antifungal with digestive targets (amphotericin B, nystatin, tioconazole, itraconazole, econazole, butoconazole, and the like),

- medicaments for digestive functional disorders (e.g.: cisapride) and for intestinal transit,

- intestinal antibacterials (aminoglycosides, nitroimidazoles, polymyxines, and the like) and antivirals (e.g.: acyclovir),

- products recognized for their soothing and/or cicatrising properties such as: biotin, polyphenols, glycyrrhizinic acid, thymol, eucalpytol, and the like, and extracts of plants rich in glycyrrhetinic acid, pantothenol, allantoin and derivatives,

- vitamins: of group B (B1, B6, B12), nicotinamide, biotin, pantothenic acid,

- products correcting hypoptyalism and regulating saliva secretion: pilocarpine, anetholtrithione,

- peptides and enzymes: elastin, collagen, glutathione, catalase, endonuclease, which can contribute to the repair of tissues lesioned by irradiation.

The following examples illustrate the present invention.

I - <u>Compositions for the buccal mucous membrane</u>

Without being limiting, and to illustrate the invention, the following preparations may be presented as examples:

	Percentages			
Examples	1	2	3	4
Water-soluble rutoside	2 to 10	2 to 10	2 to 10	2 to 10
Pilocarpine hydrochloride	---	1 to 5	---	1 to 5
Poloxamer 407	14.0	5 to 20	5 to 20	5 to 20
HPMC	1 to 3	1 to 3	1 to 3	1 to 3
Flavouring	0.1 - 0.5	0.1 to 0.5	0.1 - 0.5	0.1 to 0.5
Alpha-tocopherol	---	---	0.01 to 0.05	0.01 to 0.05
Buffer pH 7.8 qs	100	100	100	100

These compositions constitute solutions of thermoreversible consistency: fluid at room temperature (20°-25°C), viscous at the temperature (35-37°C) of the physiological cavities. Thus, the viscosity at room temperature (25°C) of a composition combining 5 to 20% of poloxamer 407 and 1 to 3% of HPMC polymer (that is 6 to 23% of gelling agents) may be sufficiently low (150 to 300×10^{-3} Pa.s) to allow easy propulsion (by the delivery system) and then an effective gelling on the mucous membrane to be protected (by passage of the viscosity to $2000\text{-}21{,}000\times10^{-3}$ Pa.s when the temperature increases between 30 and 35°C, for example).

II - <u>Composition for the digestive mucous membrane</u>

1 - Gellable liquid composition

As nonlimiting examples, there may be mentioned:

	Percentages			
Examples	5	6	7	8
Rutoside	2 to 10	1 to 5	0 to 5	0 to 5
Amphoter-icine B	---	1 to 2.5	---	---
Miconazole	---	---	1 to 5	---
Allantoin	0 to 1	0 to 1	0 to 1	---
Biotin	0 to 0.050	0 to 0.050	0 to 0.050	0 to 0.050
Dexpanthenol	0 to 1	0 to 1	0 to 1	0 to 1
St John's wort (aqueous extract)	---	---	---	0 to 5
Kallanchoe (aqueous extract)	---	---	---	0 to 5
HPMC (Methocel E4M)	1 to 3	1 to 3	1 to 3	1 to 3
Poloxamer 407 (Lutrol F127)	6 to 20	6 to 20	6 to 20	6 to 20
Sweetener/ flavouring	qs	qs	qs	qs
Preserv-atives	qs	qs	qs	qs
Water qs	100	100	100	100

2 - Granules to be dispersed in water

At the temperature of the gastrointestinal tract, this composition forms a gel adhering to the villosities of the mucous membrane.

	(mg)			
Examples	9	10	11	12
Diosmin	500	500	500	500
Extract of Centella asiatica	---	20 to 50	---	---
Hydroxypropyl-methylcellulose (HPMC)	150	150	150	150
Xanthan gum	250	250	250	250
Calcium carbonate	1000	1000	500	---
Aldioxa*	---	---	900	---
Alcloxa**	---	---	100	---
Poloxamer 407	1500	1500	1500	1500
Aluminium hydroxide	---	---	---	400
Magnesium hydroxide	---	---	---	400
Flavouring	qs	qs	qs	qs
Xylitol	1000	1000	1000	1000

*dihydroxyaluminium allantoinate

**chlorhydroxyaluminium allantoinate

(for one sachet to be dispersed in a volume of 100 to 200 ml of water)

EXAMPLE 13 - Granule to be dispersed in water (preparation for immediate use):

At the temperature of the gastrointestinal tract, this composition, in mg for one sachet to be dispersed in 100 ml of water at the time of use, also forms a gel adhering to the villosities of the mucous membrane:

OPC*	200-500
Alpha-lipoic acid	0-20
Polyvidone	200
β-cyclodextrin	1000-3000
Hydroxypropylmethylcellulose	100
Poloxamer 407	1000
Flavouring/sweetener	qs

*procyanidolic oligomers (extract of grape seed and of pine bark).

III - Composition for the rectal mucous membrane

Two examples of ready-to-use thermogellable viscous solutions are given below:

Examples	18 (in %)	19 (in %)
Rutosides	2 to 10	1 to 5
Dexpanthenol	---	1 to 5
Butylated hydroxytoluene	---	1 to 10
Alpha-tocopherol	---	0.01 to 0.05
(HPMC) Methocel E 4M	1 to 3	1 to 3
Poloxamer 407	5 to 20	5 to 20
Purified water qs	100	100

IV - Compositions for the vaginal mucous membrane

Three nonlimiting examples of solutions which gel at the temperature of the mucous membrane are given below:

Examples	20 (in %)	21 (in %)	22 (in %)
Rutosides	0.5 to 10	0.5 to 10	0.5 to 10
Butoconazole nitrate	1 to 5	---	---
Econazole nitrate	---	1 to 3	---
Thioconazole	---	---	2 to 5
Poloxamer 407	6 to 20	6 to 20	6 to 20
Methocel E 4M	1 to 2	1 to 2	1 to 2
Purified water qs	100	100	100

CLAIMS

1. Pharmaceutical composition intended to adhere to a mucous membrane in particular for the prevention and treatment of radiomucositis, and of chemomucositis induced by radiotherapy and combined radiochemotherapy, comprising an effective quantity of a compound having anti-free radical activity in the form of a mixture with a vehicle which is liquid at room temperature and which gels at the temperature of the mucous membrane and which is capable of adhering to the mucous membrane because of its gelled state.

2. Composition according to Claim 1 whose vehicle is an aqueous vehicle and comprises a mixture of 0.05 to 5% (preferably 0.1 to 3%) by weight of an agent conferring viscosity and of 1 to 20% (preferably 5 to 20%) by weight of an agent modifying the viscosity according to the temperature.

3. Composition according to Claim 2, in which the agent modifying the viscosity according to the temperature is chosen from poloxamers, poloxamines, and divinylbenzenesorbitol compounds.

4. Composition according to any one of the preceding claims, in which the anti-free radical compound is chosen from flavonoids, isoflavonoids, tocopherols, polyphenols and plant extracts containing polyphenols, vitamins (vitamins of group B in particular) and the active fractions of vegetable oils.

5. Composition according to Claim 4, in which the flavonoid is chosen from rutoside, diosmin, quercitrin, tangeretin and hesperidin.

6. Composition according to Claim 4, in which the isoflavonoid is genistin, daidzin or glycitin.

7. Composition in solid form and forming a composition according to any one of Claims 1 to 6 by mixing with water.

8. Use of a compound having anti-free radical activity in the form of a mixture with a vehicle which is liquid at room temperature and which gels at the temperature of a mucous membrane and which is capable

of adhering to this mucous membrane because of its gelled consistency, for the manufacture of a pharmaceutical composition intended for the prevention and for the treatment of radiomucositis and of chemomucositis.

9. Method for the prevention and treatment of radiomucositis and of chemomucositis induced by radiotherapy and combined radiochemotherapy, comprising the administration of a composition according to Claim 1.

10. Method according to Claim 9 for the prevention and treatment of gingival and oropharyngeal radio mucositis.

11. Method according to Claim 9 for the prevention and treatment of anorectal radiomucositis.

12. Method according to Claim 9 for the prevention and treatment of vaginal radiomucositis.

DECLARATION AND POWER OF ATTORNEY U.S.A.

ALL PATENTS, INCLUDING DESIGN
FOR APPLICATION BASED ON PCT; PARIS CONVENTION;
NON PRIORITY; OR PROVISIONAL APPLICATIONS

FOR ATTORNEYS' USE ONLY

ATTORNEYS' DOCKET NO.

101 / 102

As a below named inventor, I declare that my residence, post office address and citizenship are stated below next to my name, the information given herein is true, that I believe that I am the original, first and sole inventor (if only one name is listed at 201 below), or an original, first and joint inventor (if plural inventors are named below at 201-203, or on additional sheets attached hereto) of the subject matter which is claimed and for which patent is sought on the invention entitled:

which is described and claimed in: [X] PCT International Application No. PCT/FR99/01760 filed 19/07/1999

[ ] the attached specification [ ] the specification in application Serial No. _____ filed _____

(if applicable) and amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.
I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.
I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

103 / 104

Prior Foreign Application(s) (Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed Yes	No
98 09 230	FRANCE	July 20, 1998	[X]	[ ]
			[ ]	[ ]
			[ ]	[ ]

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Application No. _____ Filing Date _____ Application No. _____ Filing Date _____

105

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.)	(Filing Date)	(Status: patented, pending, abandoned)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys (Registration No.) to prosecute this application, receive and act on instructions from my agent, and transact all business in the Patent and Trademark Office connected therewith. HARVEY B. JACOBSON, JR. (20,851); D. DOUGLAS PRICE (24,514); JOHN CLARKE HOLMAN (22,769); MARVIN R. STERN (20,640); ALLEN S. MELSER (27,215); MICHAEL R. SLOBASKY (26,421); JONATHAN L. SCHERER (29,851); IRWIN M. AISENBERG (19,007); WILLIAM E. PLAYER (31,409); YOON S. HAM (45,307) and NATHANIEL A. HUMPHRIES (22,772)

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*Inventor(s) name must include at least one unabbreviated first or middle name.

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I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that thes statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the Unite States Code; and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201*	SIGNATURE OF INVENTOR 202*	SIGNATURE OF INVENTOR 203*
BESSE Jérôme	NGUYEN Tam	LEYDER Joëlle
DATE 18/12/00	DATE 18/12/00	DATE 18/12/00

[ ] Additional inventors are named on separately numbered sheets attached hereto.